Maternal viral load and rate of disease progression among vertically HIV-1-infected children: an international meta-analysis

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Objective: To evaluate whether maternal human immunodeficiency virus type 1 (HIV-1) RNA levels in the serum/plasma of mothers at or close to the time of delivery affects the rate of disease progression among vertically HIV-1-infected children and whether it correlates with other parameters affecting infant disease progression.

Methods: International meta-analysis of eight studies with 574 HIV-1 infected infants with available maternal HIV-1 RNA measurements at or close to delivery and clinical follow-up. The primary outcome was disease progression (stage C disease or death, n = 178). Cohort-stratified Cox models were used.

Results: Higher maternal HIV-1 RNA level at or close to delivery significantly increased disease progression risk [hazard ratio (HR), 1.25; 95% confidence interval (CI), 1.04–1.52 per 1 $\log_{10}$ increase; $P = 0.02$) with a borderline effect on mortality (HR, 1.26; 95% CI, 0.96–1.65; $P = 0.10$]. The association with disease progression risk was strong in the first 6 months of life (HR, 1.77; 95% CI, 1.28–2.45; $P = 0.001$), but not subsequently (HR, 1.03; 95% CI, 0.81–1.30). Maternal HIV-1 RNA, early infant HIV-1 RNA (at 30–200 days after birth) and infant CD4 were independent predictors of disease progression in the first 6 months. Maternal HIV-1 RNA at or close to delivery correlated with early infant HIV-1 RNA ($r = 0.26$, $P < 0.001$). Effects were independent of maternal and infant treatment.

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Conclusions: Higher maternal HIV-1 RNA at or close to delivery strongly predicts disease progression for HIV-1-infected infants, especially in their first 6 months of life and correlates with the early peak of viremia in the infected child.

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Introduction

Maternal human immunodeficiency virus type 1 (HIV-1) RNA levels in the serum or plasma are a major determinant of the risk of vertical HIV-1 transmission [1–4]. Moreover, some investigators have suggested that even among HIV-1-infected infants, disease progression may be delayed when maternal viremia is maintained at lower levels during pregnancy and delivery [5–7]. Due to the difficulties of assembling and following prospectively large numbers of HIV-1-infected children, prior investigations addressing this issue have included limited numbers of children. In addition, variability in definitions of disease progression, analytical methods and eligibility of RNA measurements poses difficulties in the comparative interpretation of the evidence. Moreover, the postulated mechanism of protection of the HIV-1-infected child against disease progression in the face of low maternal viremia is unknown. It is unclear whether maternal HIV-1 RNA levels at or close to delivery affect other determinants of the rate of disease progression, such as the levels of HIV-1 RNA in the infant early in life [8–11].

To clarify these issues, we performed an international meta-analysis including data on 574 individual mother–infant pairs with detailed, standardized information on maternal viral load at or close to delivery and several other maternal, gestational, and infant factors that determine disease progression among HIV-1-infected children.

Methods

Eligible studies

The project was designed as a meta-analysis of individual patient data [12,13] including USA and European cohorts with prospective data on the clinical outcome of vertically HIV-1-infected children along with measurements of maternal HIV-1 RNA (plasma or serum) at or close to delivery. Study teams were identified through MEDLINE searches and communications with experts. We are aware of only one published study with 31 infected children that could not be included in the meta-analysis due to non-participation of its investigators [7]. Databases were assembled according to the common meta-analysis definitions at the coordinating center [12]. Potential logical inconsistencies for specific data items were clarified through queries to the primary investigators.

Outcomes

The primary outcome for disease progression was the development of stage C disease (per CDC definition [14]) or death. The secondary outcome was death. For each child we recorded the dates of birth, last follow-up (death or censoring), and stage C diagnoses.

Database and definitions

Each participating study contributed information on all mother–infant pairs for which there was at least one eligible maternal viral load measurement and any follow-up of the infant for ascertaining disease progression. We collected information on all available maternal RNA measurements and their dates. Eligible values were the ones obtained during pregnancy or within 1 month of delivery. Later values were excluded, because maternal RNA may increase postpartum [15]. When multiple eligible values were available, the rule was to use the value closest to delivery within 6 days of delivery. If no such value was available, we used the latest value obtained during the course of pregnancy; then, as a last choice, the earliest postpartum measurement obtained 7–30 days postpartum.

We also collected information on maternal CD4 cell count at or close to delivery (using the same selection rules as for maternal RNA), and on maternal clinical AIDS diagnosis before delivery (stage C [16]). For each infant, we recorded the earliest HIV-1 RNA measurement during the window of 30–200 days after birth. We excluded measurements during the first month, because viremia increases rapidly during the first month of life, but remains fairly stable for the next 6 months [8,9]. We also recorded the earliest infant CD4 and CD8 cell counts in the same time window and whether the infant developed stage B disease [14] within 6 months after birth. Recorded gestational and obstetric factors included gestational age, birthweight, duration of rupture of membranes, mode of delivery, chorioamnionitis (as defined in each study), and multiple gestation. Maternal and infant antiretroviral treatment during the first 6 months was also recorded.

Analysis

Characteristics were summarized per study and across the meta-analysis with median and interquartile range (IQR) for continuous variables and percentages for discrete variables. HIV-1 RNA values were $\log_{10}$-transformed. Values below detection were imputed at half the threshold of detection for the specific assay.

Kaplan–Meier plots were constructed per study splitting the maternal RNA at or close to delivery according to the categories < 1000, 1000–9999, 10 000–99 999, $> 100\,000$ copies/ml and analyses was performed using the log-rank test adjusting for trend [17]. In the absence of gross violation of proportional hazards on visual inspection of the plots, the main analysis used Cox regression [18] stratified per cohort with maternal RNA values as a continuous variable. The main analyses included all follow-up. Sensitivity analyses censored data at 30 June 1997 to minimize the impact of highly active antiretroviral therapy [19]. Protease inhibitors were first marketed for pediatric use in the US in March 1997 and European licensing was fairly similar, therefore we allowed an additional 3-month period before their use might increase substantially. Furthermore, we estimated study-specific hazard ratios (HRs) for each outcome and examined between-study heterogeneity in the HR estimates using the Q statistic for general variance models [20]. We also examined whether the strength of the association between maternal HIV-1 RNA and infant disease progression was different in the first 6 months of life versus during subsequent follow-up.

Separate univariate Cox regression analyses examined also the potential relationship between the risk of progression to stage C disease or death and each of the other recorded maternal, infant, and gestational/obstetric parameters listed above. Treatment parameters included maternal antiretroviral treatment at the time of delivery, the number of drugs received by the mother until delivery, and whether the infant had received antiretroviral prophylaxis (monotherapy for 45 days or less), any other antiretroviral therapy, or any protease inhibitor during the first 3 months of life. Statistically significant ($P < 0.05$) parameters in univariate models were considered in multivariate regression with backward selection of variables per likelihood ratio criteria.

Finally, we evaluated with Pearson correlation coefficients whether the maternal HIV-1 RNA levels correlated with early infant HIV-1 RNA levels and other recorded risk factors of disease progression. The main analysis included all mother–infant pairs with available measurements. We also performed analyses excluding cases where the measurements of early infant RNA might have been affected by the institution of antiretroviral treatment and separate analyses for cases where mothers were or were not receiving antiretroviral treatment at the time of delivery. Correlation analyses were performed in the pooled meta-analysis database. Differences in the methods of RNA measurements between studies may create spurious correlations during pooling. Therefore, we also examined correlation coefficients for each separate study, evaluated between-study heterogeneity and then synthesized the study-specific coefficients weighting by the inverse of the variance and using Fisher's hyperbolic tangent transformation [21]. In the absence of significant between-study heterogeneity, fixed and random effects estimates [21] were identical and reassuringly similar to those obtained by the pooled analyses (not shown).

Analyses were performed in SPSS 10.0 (SPSS Inc., Chicago, Illinois, USA). *P*-values are two-tailed.

Results

Meta-analysis database

The meta-analysis included two randomized studies [Pediatric AIDS Clinical Trials Group (PACTG) protocols 076 and 185] and six multicenter prospective cohort studies [Enquete Perinatale Francaise-SEROGEST, Ariel, Mother and Infants Cohort Study (MICS), European Collaborative Study (ECS), Perinatal AIDS Collaborative Transmission Study (PACTS), Women and Infants Transmission Study (WITS)]. Information on maternal viral load and infant disease progression was available for all pairs of mothers and their infected infants in PACTG076, PACTG185 and Ariel, 50 of 51 cases (98%) in the French cohort (limited to data from 1997 onwards), 177 of 180 cases (98%) in WITS, 201 of 360 cases (56%) in PACTS, 38 of 50 cases (76%) in MICS, and a sample ($n = 21$) of ECS cases. Among 587 eligible mother–infant pairs, 13 had participated both in WITS and PACTG076. To avoid duplication, these cases were retained only in PACTG076, in which the available follow-up was more complete. A total of 574 eligible mother–infant pairs (range, 19–201 per study) were included in the meta-analysis (Table 1). Six studies used either the reverse transcriptase (RT)-polymerase chain reaction (PCR) method or the nucleic acid sequence-based amplification (NASBA) method for all or at least the large majority ($> 90\%$) of the RNA determinations, while the French and ECS cohorts used several methods for RNA determination. Median maternal HIV-1 RNA levels ($\log_{10}$ copies/ml) ranged between 3.73 and 4.78 across studies. The IQR for the time of measurement was 9 days prior to delivery to 2 days postpartum. Almost all measurements (557 of 574) were obtained in

Table 1. Key characteristics per study.

Study	Birth years (last follow up)	n	Maternal RNA at/close to delivery: Key method(s)	Maternal RNA at/close to delivery: Log10 copies/ml Median (IQR)	Follow-up months Median (IQR)	Child disease progression: Stage C or death n (%)	Child disease progression: Death n (%)
PACTG 076	1991–1994 (1995)	56	RT-PCR	4.15 (3.55–4.49)	18.2 (17.8–18.9)	15 (26.8)	7 (12.5)
PACTG 185	1994–1997 (1999)	24	NASBA	4.78 (4.00–5.17)	18.2 (17.8–18.6)	6 (25.0)	2 (8.3)
Ariel	1993–1995 (1998)	19	RT-PCR	3.86 (3.42–4.51)	23.1 (6.0–48.1)	5 (26.3)	2 (10.5)
French	1997–2001 (2002)	50	bDNA, RT-PCR	4.00 (2.73–4.54)	24.2 (13.9–41.5)	2 (4.0)	1 (2.0)
MICS	1985–1991 (1993)	38	RT-PCR	4.21 (3.75–4.72)	30.7 (21.4–37.8)	17 (43.6)	9 (23.1)
ECS	1989–1999 (2000)	21	NASBA, RT-PCR, Nuclisens	3.73 (3.30–4.40)	70.4 (28.4–108.9)	7 (33.3)	3 (14.3)
PACTS	1987–1998 (2000)	201	NASBA	4.08 (3.44–4.67)	47.0 (23.1–75.4)	83 (41.3)	47 (23.4)
WITS	1990–2001 (2001)	165	RT-PCR	4.44 (3.90–5.04)	18.0 (18.0–18.0)	43 (26.1)	15 (9.1)
Total	1985–2001 (2002)	574	–	4.19 (3.56–4.75)	18.3 (18.0–43.5)	178 (31.0)	86 (15.0)

PACTG, Pediatric AIDS Clinical Trials Group; French, Enquete Perinatale Francaise-SEROGEST; MICS, Mother and Infants Cohort Study; ECS, European Collaborative Study; PACTS, Pediatric AIDS Collaborative Transmission study; WITS, Women and Infants Transmission Study; IQR, interquartile range; RT-PCR, reverse transcription-polymerase chain reaction; NASBA, nucleic acid sequence-based amplification.

the last trimester or first month postpartum. Median follow-up was at least 18 months in all studies.

Disease progression occurred in 178 children. There were 86 deaths. The probability of disease progression for the included children (stage C or death) varied significantly across studies (log-rank $P = 0.027$). The variability was due to different years of enrolment across studies. There was no prominent between-study variability when separate analyses were conducted for birth years 1985–1990 (log-rank $P = 0.27$), 1991–1996 (log-rank $P = 0.30$), and 1997–2001 (log-rank $P = 0.45$) corresponding roughly to the pre-prophylaxis, prophylaxis, and highly active antiretroviral therapy eras. The proportion of children who had disease progression was 28 of 70, 140 of 398, and 10 of 100, respectively in the three birth-year periods. There was no significant between-study variability in the risk of death (log-rank $P = 0.33$). With censoring at 30 June 1997, the pooled database retained 503 children, 173 disease progression events and 85 deaths.

Table 2 presents information about other maternal, infant, gestational, obstetric and treatment characteristics. Antiretroviral therapy at the time of delivery was given to 28.4% of mothers before 1995 and in 88.5% in later years. Only 15 mothers (2.8%) received protease inhibitors. About one-third of infants received antiretroviral therapy in the first 3 months of life, but only 5.6% received a protease inhibitor in the same

Table 2. Maternal, infant, gestational/obstetric and treatment characteristics in the pooled meta-analysis database.

Characteristic	n[a]	Value
Maternal CD4 at /close to delivery, median (IQR) [cells per cubic mm]	476	395 (245–587)
Maternal stage C disease prior to delivery, n (%)	546	89 (16.3)
Early infant RNA, median (IQR) [log 10 copies/ml]	377	5.58 (4.87–6.11)
Early infant CD4, median (IQR) [cells per cubic mm]	518	2396 (1670–3316)
Early infant CD8, median (IQR) [cells per cubic mm]	517	1402 (972–2100)
Infant reached stage B before 6 months of age, n (%)	536	228 (42.5)
Gestational age, median (IQR) [weeks]	567	38 (37–40)
Birth weight, median (IQR) [g]	559	2870 (2385–3300)
Duration of ruptures of membranes, median (IQR) [hours]	486	5.0 (1.00–13.6)
Caesarean section mode of delivery, n (%)	549	141 (25.7)
Chorioamnionitis, n (%)	458	52 (11.4)
Multiple gestation, n (%)	510	12 (2.4)[b]
Maternal given antiretroviral treatment at time of delivery, n (%)	569	272 (47.8)
Mother received > 2 drugs (any time up to delivery), n (%)	553	22 (4.0)
Infant received any antiretroviral treatment in first 3 months, n (%)	574	170 (29.6)
Infant received protease inhibitor in first 3 months, n (%)	574	32 (5.6)
Infant received antiretroviral prophylaxis, n (%)	574	84 (14.6)

[a]With available information. [b]Includes eight cases where only one of multiple newborns were infected and two pairs of infected twins; each infant in a pair is counted separately in all analyses. IQR: interquartile range.

interval. Another 14.6% received antiretroviral prophylaxis. There was a significant relationship ($P < 0.001$) between maternal treatment at delivery and infant antiretroviral therapy starting in the first 3 months in the two largest cohorts (PACTS, WITS) that spanned both the pre-1995 era and subsequent time periods.

Maternal viral load as a predictor of disease progression

Study-specific analyses evaluating the relationship between maternal RNA at or close to delivery and infant disease progression should be interpreted with caution given limited sample sizes. Of the four studies with at least 10 disease progression events, three suggested an association between maternal viral load and disease progression, but formal significance was reached only for PACTG076 (log-rank adjusted for trend $P = 0.045$ for PACTG076, $P = 0.073$ for WITS, $P = 0.20$ for PACTS). No pattern was seen in MICS ($P = 0.97$).

In Cox regressions stratified per cohort, the association was formally statistically significant [hazard ratio (HR), 1.25; 95% confidence interval (CI), 1.04–1.52] per 1 $\log_{10}$ increase in viral load, $P = 0.020$). The association with mortality risk was similar, but of borderline significance (HR, 1.26; 95% CI, 0.96–1.65; $P = 0.10$). With censoring at 30 June 1997, both associations were formally statistically significant (HR, 1.32; 95% CI, 1.07–1.61; $P = 0.008$ for progression to stage C or death and HR, 1.38; 95% CI, 1.03–1.85; $P = 0.033$ for death, respectively).

There was no significant between-study heterogeneity in the HR estimates for progression to stage C or death (Fig. 1a), or for mortality (not shown). Further analysis showed that a higher maternal HIV-1 RNA significantly increased the risk of disease progression in the first 6 months of life (HR stratified per study, 1.77 per 10-fold increase; 95% CI, 1.28–2.45; $P = 0.001$), but had no significant impact after this time interval (HR stratified per study, 1.03; 95% CI, 0.81–1.30; $P = 0.56$). There was no statistically significant between-study heterogeneity in the HR estimates within each

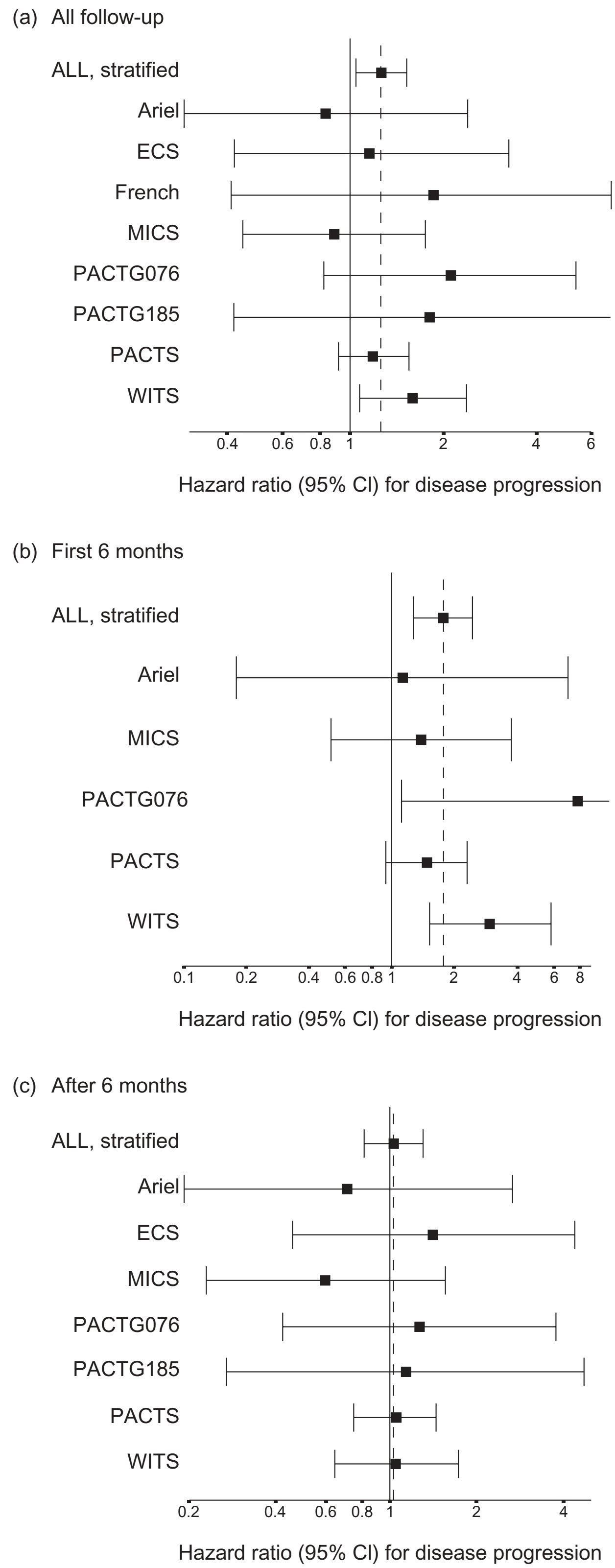

Fig. 1. Hazard ratio estimates with their respective 95% confidence intervals (CI) in each study for the association between maternal HIV-1 RNA at the time of delivery and the risk of progression to stage C or death among HIV-1 infected children. Also shown is the overall hazard ratio and 95% confidence interval obtained from a Cox model stratified per study. Hazard ratios correspond to 10-fold increase in maternal viral load. Vertical reference lines show the line of no association (continuous line) and the overall hazard ratio (discontinuous line). (a), considering all follow-up; (b), limited to the first 6 months after birth; (c), limited to follow-up after the first 6 months. Studies with less than two events in a time interval are not shown in the respective panels. PACTG, Pediatric AIDS Clinical Trials Group; French, Enquete Perinatale Francaise-SEROGEST; MICS, Mother and Infants Cohort Study; ECS, European Collaborative Study; PACTS, Pediatric AIDS Collaborative Transmission study; WITS, Women and Infants Transmission Study.

time interval (Fig. 1b and 1c). No statistically significant time-related differences were seen for the risk of death (not shown).

The association for the first 6 months was similar when data were censored at 30 June 1997 (HR, 1.75; 95% CI, 1.26–2.43; $P = 0.001$) or when further limited to children without any antiretroviral therapy in the first 3 months of life (HR, 1.71; 95% CI, 1.18–2.48; $P = 0.005$). Excluding viral loads ≥ 100 000 copies/ml, the effect was modestly smaller (HR, 1.51; 95% CI, 0.96–2.38; $P = 0.077$), suggesting a potentially excess risk at very high maternal viral loads.

Other predictors and multivariate models

In univariate analyses (Table 3), maternal viral load was the only maternal predictor significantly associated with the risk of progression to stage C or death. Maternal CD4 and disease stage had a borderline effect. Early infant HIV-1 RNA, infant CD4 cell count and progression to stage B before 6 months were strong determinants of the risk of disease progression, whereas CD8 cell count had no significant effect on disease progression. Premature infants and infants with low birth weight had a significantly higher risk of disease progression. Maternal and early infant treatment parameters had no significant effect (Table 3).

In multivariate modelling, early infant factors remained key independent predictors of disease progression (HR, 2.22; 95% CI, 1.63–3.03; $P < 0.001$ per 1 $\log_{10}$ increase in early infant HIV-1 RNA and HR, 0.97; 95% CI, 0.96–0.99; $P = 0.004$ per 100×10^6 cells/l increase in early infant CD4 cell count) along with birth weight (HR, 0.97; 95% CI, 0.94–0.99; $P = 0.012$ per 100 g increase). For the first 6 months of life, maternal HIV-1 RNA at or close to delivery (HR, 1.57 per 1 $\log_{10}$ increase; 95% CI, 0.97–2.53; $P = 0.067$), early infant HIV-1 RNA (HR, 3.01 per 1 $\log_{10}$ increase; 95% CI, 1.77–5.14; $P < 0.001$) and infant CD4 (HR, 0.97; 95% CI, 0.94–1.00; $P = 0.043$ per 100×10^6 cells/l increase) were the retained independent predictors of disease progression. Results were similar when limited to children not receiving any antiretroviral therapy in the first 3 months [HR, 1.89; ($P = 0.032$); HR, 3.15 ($P < 0.001$) and 0.96 ($P = 0.010$), respectively]. For the time interval after the first 6 months of life, independent predictors of disease progression included early infant RNA, early infant CD4 cell count, the presence of stage B disease during the first 6 months and birth weight.

Correlation of maternal viral load with other predictors of disease progression

In the pooled meta-analysis database the maternal RNA at or close to delivery significantly correlated with early infant RNA, and the correlation was of modest strength (Pearson $r = 0.26$, $P < 0.001$ based on n = 377 available mother–infant pairs). Maternal RNA was not correlated with early infant CD4 cell count ($r = -0.06$, $P = 0.19$), early infant CD8 cell count ($r = 0.05$, $P = 0.22$), stage B disease before 6 months ($r = -0.01$, $P = 0.78$), gestational age ($r = -0.01$, $P = 0.78$) or birth weight ($r = -0.01$, $P = 0.85$).

Study-specific correlations between maternal and infant RNA were consistent with the pooled result (not shown) and there was no significant between-study heterogeneity. The observed correlation remained unchanged when the analysis was limited to cases where

Table 3. Association of various parameters with the risk of progression to stage C or death according to univariate Cox models stratified per study.

Characteristic	HR (95% CI)	*P*
Maternal RNA at/close to delivery (per 1 $\log_{10}$)	1.25 (1.04–1.52)	0.02
Maternal CD4 at/close to delivery (per 100×10^6 cells/l)	0.94 (0.88–1.01)	0.07
No maternal stage C disease prior to delivery	0.69 (0.46–1.03)	0.07
Early infant RNA (per 1 $\log_{10}$)	2.30 (1.72–3.09)	< 0.001
Early infant CD4 (per 100×10^6 cells/l)	0.96 (0.94–0.97)	< 0.001
Early infant CD8 (per 100×10^6 cells/l)	1.00 (0.99–1.01)	0.78
Infant did not reach stage B before 6 months of age	0.35 (0.22–0.57)[a]	< 0.001
Gestational age (per 1 week)	0.93 (0.89–0.96)	< 0.001
Birth weight (per 100 g)	0.96 (0.94–0.98)	< 0.001
Duration of ruptures of membranes (per 1 h)	1.00 (1.00–1.00)	1.00
Caesarean section mode of delivery	1.13 (0.79–1.61)	0.50
Chorioamnionitis	1.02 (0.62–1.67)	0.93
Multiple gestation	0.75 (0.24–2.38)	0.63
Maternal antiretroviral treatment at delivery	1.10 (0.80–1.52)	0.57
Number of drugs mother received (any time) (per drug)	0.99 (0.79–1.25)	0.92
Any infant antiretroviral treatment in first 3 months	0.77 (0.51–1.16)	0.21
Any infant protease inhibitor in first 3 months	0.45 (0.14–1.41)	0.17
Infant received antiretroviral prophylaxis	0.67 (0.37–1.20)	0.18
Birth year (per year)	0.91 (0.85–0.98)	0.012

[a]Hazard ratio (HR) pertains to the time interval after 6 months of age. CI, confidence interval.

the early infant RNA had been measured before any protease inhibitor was given ($r = 0.30$, $n = 365$, $P < 0.001$), or before any antiretroviral therapy or prophylaxis was given ($r = 0.27$, $n = 233$, $P < 0.001$).

The correlation was also clearly seen among the 194 cases where the mothers were receiving antiretroviral therapy at the time of delivery ($r = 0.31$, $P < 0.001$), and separately among the 183 cases where mothers were not receiving antiretroviral therapy at the time of delivery ($r = 0.18$, $P = 0.015$) (Fig. 2). For treated mothers who achieved suppression of viremia to < 1000 copies/ml by the time of delivery on antiretroviral treatment, the early infant RNA was very low [median (in $\log_{10}$ copies/ml), 4.25; IQR, 2.55–5.79], on average more than 10-fold lower than the viral load of infants born to mothers with 1000–9999 copies/ml and the difference was larger when compared against mothers with higher levels of viremia.

Analyses limited to the 166 cases where mothers received no antiretroviral therapy at the time of delivery and infants had received no antiretroviral therapy by the time of early HIV-1 RNA measurement also showed an overall correlation coefficient of 0.23 ($P = 0.003$) with study-specific coefficients ranging between 0.12–0.56 (no significant between-study heterogeneity). Analyses limited to maternal viral load in the last trimester or first month postpartum and infant viral load 30–90 days after birth ($n = 279$) gave $r = 0.28$ ($P < 0.001$).

Discussion

This international meta-analysis combining information from eight multicenter studies clarifies that maternal HIV-1 RNA levels at or close to the time of delivery are a strong independent predictor of the early risk of disease progression in vertically HIV-1-infected infants. The effect is limited to the first 6 months of life, when the risk of infant disease progression almost doubles for each 10-fold increase in maternal HIV-1 RNA levels. No such effect was seen after the first 6 months. Moreover, maternal HIV-1 RNA levels at or close to delivery correlated with the early levels of viremia attained in the infant after the first month of life. Thus, part of the maternal viral load effect on infant disease progression may be exerted through its association with early infant viremia. However, both maternal and early infant viremia independently determined disease progression during the first 6 months.

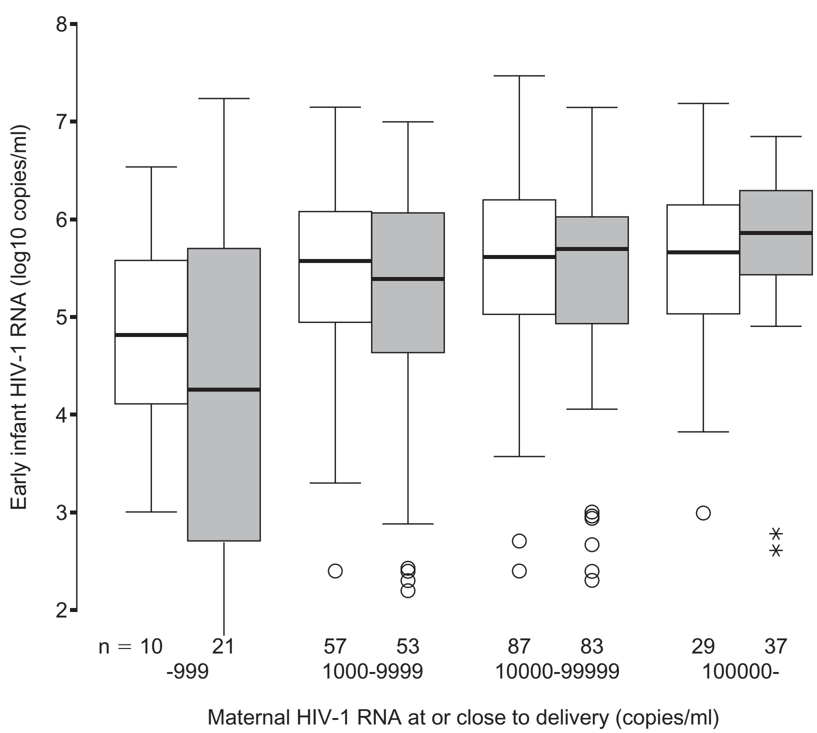

Fig. 2. Boxplots showing the correlation between maternal HIV-1 RNA at or close to delivery and early infant HIV-1 RNA in pooled analyses. Horizontal lines correspond to medians, boxes correspond to interquartile range, and whiskers to range, except for outliers (shown by circles/asterisks). White boxes: mothers not receiving antiretroviral therapy at the time of delivery. Gray boxes, mothers receiving antiretroviral therapy at the time of delivery.

Our results show at least a partial symmetry between maternal and early infant viremia. The parameters that dictate the evolution of viral replication during infancy and early childhood are not fully understood. Viral load increases during the first month after birth, stabilizes for about 6 months, and declines afterward [8,9,22], a distinct pattern compared with adults [23]. Both the height of the early peak and the subsequent decline show individual variability [24]. We limited our attention to the early peak, which correlated modestly with maternal HIV-1 RNA levels. This may reflect some similarity in immunologic factors, viral strains, and/or genetic factors between the mother and the infant. Maternal viral load may show a stronger correlation with infant viremia during the first three months than in subsequent time [25]. Moreover, measurements below detection lead to an underestimation of the true correlation [25], but such measurements accounted for $< 4\%$ of our database.

Maternal factors that regulate the maternal 'setpoint' of viremia may be important for regulating the early 'setpoint' for the HIV-1-infected child as well. The immune system of the infant is still immature and may depend on the passive transfer of maternal antibodies or other maternal factors for containing viral replication. The immune milieu of the infant in the early months of life may reflect to a considerable extent the maternal immune milieu, therefore maternal viral load has predictive value for the risk of disease progression both in the mother and in the newborn. With the maturation of the immune system in late infancy and beyond, the immunologic containment may depend more on the immune response of the child, translating to variable slopes of decay of viral load and a consequent loss of the predictive power of maternal viral load. Besides immunologic factors, mothers and their infants may occasionally share the same strain of infecting virus.

Genetic similarity between mothers and infants should also be considered. For example, the $\Delta32$ mutation in the CCR5 gene is associated both with the levels of viremia and the risk of disease progression in adults [26] and may have similar effects in children [27], although it may not affect the risk of perinatal transmission [28]. Moreover, these genetic effects may also be time-limited and viral evolution bypasses them during the course of the infection [29].

Some limitations of this meta-analysis should be acknowledged. Despite the effort to include all eligible studies, some data may have eluded our attention. Nevertheless, the assembled database was sufficiently powered. Another issue is that some heterogeneity across the included cohorts is unavoidable. We took meticulous care to standardize definitions across studies. Consistency of definitions is an advantage of a meta-analysis using individual patient data [13]. Some parameters were impossible to homogenize, in particular RNA measurements were performed with different assays across different studies. We used stratified models and tested for between-study heterogeneity in order to respect such potential differences. Furthermore, the included RNA measurements were performed in very experienced multicenter studies with meticulous systems for quality assurance. Random, non-systematic errors would tend to decrease the observed association between maternal and infant viral loads. Missing data (infants without maternal viral load measurements) might also affect the results, but would probably not introduce a systematic bias in a specific direction for the observed association.

Finally, antiretroviral therapy, especially highly active regimens may affect both viral load measurements and the risk of disease progression [30,31]. In order to avoid a confounding effect, we also performed analyses limited to the era before protease inhibitors. The results were very consistent with the analysis including all available follow up. Moreover, we found no major differences in the correlation between maternal and early infant viremia in treated vs. untreated cases.

Maintaining low levels of maternal viremia at the time of delivery may provide an added beneficial effect on infant disease progression, beyond the reduction in the risk of vertical transmission [1–4] and maternal disease progression [23]. Other maternal factors such as disease stage [32] may be less important, if mothers are adequately treated. The risk of vertical HIV-1 transmission is currently very low for mothers who achieve adequate suppression of viremia [2]. For such cases, even if the virus is eventually transmitted, our findings suggest that the early viral burst in the infant is likely to be less prominent and the risk of disease progression in the infant may be considerably curtailed. This would be another argument in favor of aggressive treatment of pregnant women with regimens that achieve sufficient suppression of viral replication [33].

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References

1. Contopoulos-Ioannidis DG, Ioannidis JP. **Maternal cell-free viremia in the natural history of perinatal HIV-1 transmission: a meta-analysis.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1998; **18**:126–135.
2. Ioannidis JP, Abrams EJ, Ammann A, Bulterys M, Goedert JJ, Gray L, *et al*. **Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads < 1000 copies/ml.** *J Infect Dis* 2001; **183**:539–545.
3. Mofenson LM, Lambert JS, Stiehm R, Bethel J, Meyer WA, Whitehouse J, *et al*. **Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine.** *N Engl J Med* 1999; **341**:385–393.
4. Garcia PM, Kalish LA, Pitt J, Minkoff H, Quinn TC, Burchett SK, *et al*. **Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission.** *N Engl J Med* 1999; **341**:394–402.
5. Rich KC, Fowler MG, Mofenson LM, Abboud R, Pitt J, Diaz C, *et al*. **Maternal and infant factors predicting disease progression in human immunodeficiency virus type 1-infected infants.** *Pediatrics* 2000; **105**:e8.
6. Lambert G, Thea DM, Pliner V, Steketee RW, Abrams EJ, Matheson P, *et al*. **Effect of maternal CD4+ cell count, acquired immunodeficiency syndrome, and viral load on disease progression in infants with perinatally acquired human immunodeficiency virus type 1 infection.** *J Pediatr* 1997; **130**:890–897.
7. Dickover RE, Dillon M, Leung KM, Krogstad P, Plaeger S, Kwok S, *et al*. **Early prognostic indicators in primary perinatal human immunodeficiency virus type 1 infection: importance of viral RNA and the timing of transmission on long-term outcome.** *J Infect Dis* 1998; **178**:375–387.
8. Shearer WT, Quinn TC, LaRussa P, Lew JF, Mofenson L, Almy S, *et al*. **Viral load and disease progression in infants infected with human immunodeficiency virus type 1.** *N Engl J Med* 1997; **336**:1337–1342.
9. Abrams EJ, Weedon J, Steketee RW, Lambert G, Bamji M, Brown T, *et al*. **Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants.** *J Infect Dis* 1998; **178**:101–108.
10. Mofenson LM, Harris DR, Rich K, Meyer WA 3rd, Read JS, Moye J Jr, *et al*. **Serum HIV-1 p24 antibody, HIV-1 RNA copy number and CD4 lymphocyte percentage are independently associated with the risk of mortality in HIV-1-infected children.** *AIDS* 1999; **13**:31–39.
11. Kalish LA, McIntosh K, Read JS, Diaz C, Landesman SH, Pitt J, *et al*. **Evaluation of human immunodeficiency virus (HIV) type 1 load, CD4 T cell level, and clinical class as time-fixed and time-varying markers of disease progression in HIV-1-infected children.** *J Infect Dis* 1999; **180**:1514–1520.

12. Stewart LA, Clarke MJ. **Practical methodology of meta-analyses (overviews) using updated individual patient data.** *Stat Med* 1995; **14**:2057–2079.
13. Ioannidis JP, Rosenberg PS, Goedert JJ, O'Brien TR. **Meta-analysis of individual participants' data in genetic epidemiology.** *Am J Epidemiol* 2002; **156**:204–210.
14. Centers for Disease Control and Prevention. **1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age.** *MMWR* 1994;**43 (RR-12)**:1–10.
15. Cao Y, Krogstad P, Korber BT, Koup RA, Muldoon M, Macken C, *et al*. **Maternal HIV-1 viral load and vertical transmission of infection : the Ariel project for the prevention of HIV transmission from mother to infant.** *Nat Med* 1997; **3**:549–552.
16. Centers for Disease Control and Prevention. **1993 revised classification system for HIV infection and expanded surveillance case definition for aIDS among adolescents and adults.** *MMWR* 1992; **41**:1–19.
17. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York : John Wiley; 1980.
18. Cox DR. **Regression models and life tables (with discussion).** *J R Stat Soc Series B* 1972; **34**:187–220.
19. Bernardi S, Thorne C, Newell ML, Giaquinto C, Tovo PA, Rossi P. **Variable use of therapeutic interventions for children with human immunodeficiency virus type 1 infection in Europe.** *Eur J Pediatr* 2000; **159**:170–175.
20. Pettiti D. *Meta-analysis, Decision-analysis, and Cost-effectiveness Analysis*. 2nd edn. New York: Oxford University Press; 1999.
21. Cooper H, Hedges LV. *The Handbook of Research Synthesis*. New York: Russell Sage Foundation; 1994.
22. European Collaborative study. **Level and pattern of HIV-1-RNA viral load over age: differences between girls and boys?** *AIDS* 2002; **16**:97–104.
23. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. **Prognosis in HIV-1 infection predicted by the quantity of virus in plasma.** *Science* 1996; **272**:1167–1170.
24. Engels EA, Rosenberg PS, Katki H, Goedert JJ, Biggar RJ. **Trends in human immunodeficiency virus type 1 (HIV-1) load among HIV-1-infected children with hemophilia.** *J Infect Dis* 2001; **184**:364–368.
25. Wiener J, Lyles R, Abrams E, Palumbo P, Nesheim S, Vink P, *et al*. **Early dynamics of RNA viral load levels in HIV-infected infants and their correlations to maternal RNA viral load around delivery.** In: *Program and Abstracts of the 9th Conference on Retroviruses and Opportunistic Infections*, Seattle, Feb. 2002. American Society for Microbiology.
26. Ioannidis JPA, Rosenberg PS, Goedert JJ, *et al*. for the International Meta-analysis of HIV Host Genetics. **Effects of CCR5-Δ32, CCR2-64I and SDF-1 3′A polymorphisms on HIV disease progression: an international meta-analysis of individual patient data.** *Ann Intern Med* 2001; **135**:782–795.
27. Misrahi M, Teglas JP, N'Go N, Burgard M, Mayaux MJ, Rouzioux C, *et al*. **CCR5 chemokine receptor variant in HIV-1 mother-to-child transmission and disease progression in children.** *JAMA* 1998; **279**:277–280.
28. Contopoulos DG, O'Brien TR, Rosenberg PS, Goedert JJ, Ioannidis JPA. **Effect of CCR5-Δ32 heterozygosity on the risk of perinatal HIV-1 transmission.** *J Acquir Immune Defic Syndr* 2003; **32**:70–76.
29. Mulherin SA, O'Brien TR, Ioannidis JP, Goedert JJ, Buchbinder SP, Coutinho RA, *et al*. **Effects of CCR5-delta 32 and CCR2-64I alleles on HIV-1 disease progression: the protection varies with duration of infection.** *AIDS* 2003; **17**:377–387.
30. European Collaborative Study. **Fluctuations in symptoms in HIV-infected children: the first 10 years of life.** *Pediatrics* 2001; **108**:116–122.
31. Abrams EJ, Wiener J, Carter R, Kuhn L, Palumbo P, Nesheim S, *et al*. **Maternal health factors and early pediatric antiretroviral therapy influence the rate of perinatal HIV-1 disease progression in children.** *AIDS* 2003; **17**:867–877.
32. Blanche S, Mayaux MJ, Rouzioux C, Teglas JP, Firtion G, Monpoux F, *et al*. **Relation of the course of HIV infection in children to the severity of the disease in their mothers at delivery.** *N Engl J Med* 1994; **330**:308–312.
33. US Public Health Service Task Force. **Recommendations for use of antiretroviral drugs in pregnant HIV-1infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States.** http://www.hivatis.org, version updated August 30, 2002).